American Journal of Pathology, Vol. 142, No. 5, May 1993

Lymphocytes Infiltrating Primary Cutaneous Neoplasms Selectively Express the Cutaneous Lymphocyte-Associated Antigen (CLA)

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The cutaneous lymphocyte-associated antigen (CLA) is the T-cell ligand for E-selectin and is involved in tissue selective migration of memory/effector T cells to chronic inflammatory sites in skin. Here, we examine the hypothesis that CLA is also involved in the local host immune response to cutaneous neoplasms. Eleven primary cutaneous melanomas, nine primary cutaneous squamous cell carcinomas, and 11 assorted neoplasms metastatic to cutaneous and noncutaneous sites were immunostained with anti-CLA (HECA-452), as well as antibodies directed against B cells (CD20), T/NK cells (CD43), and memory/effector T cells (CD45RO). Essentially all of the lymphocytes surrounding and infiltrating both the cutaneous and noncutaneous tumors were CD43+/CD20−, and most expressed the memory/effector marker CD45RO. CLA was expressed on 10 to 80% (mean: 50%) of T cells associated with primary cutaneous neoplasms (including both melanomas and squamous cell carcinomas) but was essentially absent from noncutaneous primaries (including those metastatic to dermis) and from cutaneous primaries metastatic to dermis or other sites. Overall, the results suggest that CLA + memory T cells are a major component of the local host immune response to cutaneous neoplasms and are likely recruited to the skin by site-specific rather than tumor-specific mechanisms. The lack of a CLA + T-cell response to dermal metastases suggests that epidermal involvement may be required to attract this subset. (Am J Pathol 1993, 142: 1556–1564)

The migration of lymphocytes from blood to tissues is a critical element of the immune/inflammatory response and determines, to a great extent, the admixture of immunoreactive cells available at any given site. Recent work has characterized the complex physiology of this process and has identified some of the molecular mechanisms responsible for this physiology.[1] Following chronic inflammatory stimuli, tertiary (extralymphoid) sites such as the skin preferentially recruit monocytes and CD45RO+ memory/effector T cells. However, not all memory/effector T cells extravasate at all tertiary sites, but rather, the memory subset is composed of multiple subsets with tissue-selective homing behavior. With regard to skin, expression of cutaneous lymphocyte-associated antigen (CLA) defines a novel subset of memory T lymphocytes with a predilection for the skin.[2–4] CLA is expressed by the vast majority of memory T cells in skin, a subset of peripheral blood memory T cells, and few T cells in extracutaneous sites. Recent work indicates CLA is the T-cell ligand for the vascular adhesion molecule E-selectin, which, in the setting of chronic inflammation, is preferentially expressed in skin.[5] Thus, CLA and E-selectin seem to function as a homing receptor/endothelial ligand pair involved in skin-selective T-cell homing.

The characterization of the role CLA plays in T-cell recruitment to inflammatory dermatoses offers a unique opportunity to investigate mechanisms involved in the recruitment of T cells to tumors. It is possible that tumors provide unique microenvironments capable of recruiting novel lymphocyte subsets, or alternatively, these lesions might elicit inflammatory infiltrates similar or identical to those elicited by non-neoplastic inflammatory stimuli at the same sites. With regard to cutaneous neoplasms, the latter possibility would predict the selective presence of a high proportion of CLA+ T cells associated with these tumors, analogous to the situation with non-

Supported in part by grants AI 31545, CA 34233, CA 33119, and AI 19957 from the National Institutes of Health.

Accepted for publication October 26, 1992.

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neoplastic inflammatory infiltrates. If instead, tumors were to constitute unique sites, one would not expect the CLA+ T-cell subset to be a major component of the inflammatory infiltrate.

To determine the prevalence of CLA-expressing cells in the local host immune response to cutaneous neoplasms, we employed paraffin section immunohistology to compare the phenotypic profile of lymphocytes responding to two different categories of primary cutaneous neoplasms—malignant melanoma and squamous cell carcinoma—to that of noncutaneous primaries and metastatic lesions. A pan T-cell/NK-cell marker (Leu-22/CD43), a memory/effector T-cell marker (OPD4/CD45RO), and a pan B-cell marker were studied along with CLA (HECA-452) to provide a context for the CLA reactivity.[6,7]

Materials and Methods

Case Selection

Eleven consecutive primary cutaneous melanomas and nine consecutive primary cutaneous squamous cell carcinomas were collected retrospectively from the Surgical Pathology files at Stanford University. Four primary neoplasms of skin metastatic to other sites were also assembled. These consisted of one cutaneous squamous cell carcinoma metastatic to a lymph node, and two malignant melanomas metastatic to subcutaneous tissues, and one to the small intestine. Also studied were a cutaneous squamous cell carcinoma and a malignant melanoma, each metastatic to another cutaneous (dermal) site. Three cases of noncutaneous primaries metastatic to the dermis were also examined. The latter included one squamous cell carcinoma of the lung and two of the head and neck. The control group tumors were small nonulcerated lesions measuring no more than 1.0 cm. These patients were clinically well at the time localized cutaneous metastases were documented and had not received recent radiotherapy or chemotherapy. An adenocarcinoma of the colon and an adenocarcinoma of the stomach metastatic to lymph nodes were also included as controls. Two of us (AG and BS) reviewed all the cases. Each lesion had a typical clinical and histological presentation.

Immunohistochemistry

Sections of paraffin-embedded, formalin-fixed tissues were stained with a biotin-streptavidin immunohistochemical method.[8] To summarize, 5-μ-thick sections were deparaffinized and rehydrated. Endogenous peroxidase was blocked with 3% H_2O_2 for 5 minutes. Sections were then incubated with appropriately titered monoclonal antibodies, either L26/CD20 (Dako, Santa Barbara, CA), Leu-22/CD43 (Becton-Dickinson, Mountain View, CA), OPD4 (Dako), HECA-452/CLA, or isotype-matched controls at room temperature for 30 minutes.[2] This was followed by incubation with a biotinylated goat second-stage antibody directed against mouse IgG or rat IgM (Jackson Immunoresearch Laboratories Inc., West Grove, PA) for 45 minutes at 4 C and then with peroxidase-conjugated streptavidin for 45 minutes at 4 C. Diaminobenzidine was used as the chromogen, and methanol was used to fix the precipitate. Each step was followed by a rinse in phosphate-buffered saline. Finally, the sections were lightly counterstained with hematoxylin, dehydrated, and coverslipped.

Scoring

Scoring of the markers was performed by two observers (AG and BS) using an Olympus BH-2 light microscope equipped with an ocular reticle (magnification, ×15) and a ×60 objective. We evaluated the most evenly labeled regions with an extensive immune response to tumor. When a tumor mass was present, lymphocytes at the center of the lesion were scored separately from those at the periphery if a difference in the percentage of cells staining was apparent. We counted as positive lymphocytes showing clear-cut reactivity above background with localization appropriate for the antibody. The percentages of lymphocytes staining with each antibody were independently estimated then averaged. Interobserver variability was within ±10%.

Statistical Analysis

Kramer's modification of the Tukey multiple comparison test was used to compare the mean percentage of cells demonstrating a specified immunoreactivity between each of several histological groups.[9,10] This method tests for differences between group means by using the Studentized difference between the largest and smallest means (q distribution) as a measure of their dispersion.[11] Results were obtained using JMP version 2.02 software (SAS Institute Inc., Cary, NC) for the Apple MacIntosh. An overall α-level of 0.05 was used.

Results

The immune response to cutaneous tumors was evaluated away from areas of ulceration or necrosis.

It consisted predominantly of lymphocytes in all lesions. The lymphocytes were primarily small cells with relatively few large or activated cells. In some lesions, scattered plasma cells or histiocytes were observed. Immunohistochemical profiles of each case and corresponding summary data are shown in Table 1. Baseline immunohistochemical studies revealed that the vast majority of cells surrounding and infiltrating the tumors marked as T or NK cells. Leu-22 (CD43) reactivity ranged from 85 to 100% for both primary cutaneous neoplasms with means exceeding 95% and correspondingly small standard deviations (Figure 1). In the metastatic tumor control groups, 82.5% to 98.8% of infiltrating lymphocytes stained with Leu-22. Only scattered $L26^+$ (CD20) B cells were identified, except in the gastrointestinal adenocarcinomas metastatic to lymph nodes, where it is difficult to completely exclude residual nodal B cells.

Most of the infiltrate in the primary cutaneous neoplasms marked as a memory T-cell subset (Figure 2). Staining with OPD4 ranged from 25 to 80% (mean 54.0 ± s.d. 19.1) for primary malignant melanomas. Among primary squamous cell carcinomas, the percentage of positive cells was nearly identical, ranging from 20% to 90% (mean 55.0 ± s.d. 28.5). It was difficult to evaluate for tumor infiltrating lymphocytes because there were no large tumor masses in the dermis.

The percentages of lymphocytes staining as T-memory subset in the non-nodal metastatic controls group were similar on average to the primary cutaneous neoplasms. There were differences in nodal metastases, but these probably reflect the resident lymphoid population. Nevertheless, an interesting trend emerged when the lymphocyte populations at the periphery and within the tumors were scored separately. Anywhere from 63.3% to 82.5% of the peripheral lymphocytes marked as a T-memory subset. In contrast, the majority of central tumor infiltrating lymphocytes did not clearly mark as a T-memory subset, providing indirect support for a population of virgin T cells or, more likely, natural killer cells (which also bear CD43).[12]

The proportion of lymphocytes expressing CLA was similar in primary cutaneous squamous cell carcinomas and melanomas but markedly different from the other categories (Table 1 and Figure 3). Staining at the periphery and within the neoplasms by HECA-452 ranged between 15 to 80% (mean 48.6 ± s.d. 21.1) for primary malignant melanomas. Likewise, the range was 10 to 80% (mean 45.0 ± s.d. 19.3) for primary squamous cell carcinomas. The immune response to dermal and noncutaneous metastases of primary skin neoplasms, cutaneous metastases of non-cutaneous primaries, and the other metastatic tumor groups consisted predominantly of uniformly CLA-negative T-memory lymphocytes. The Tukey-Kramer test confirmed that the differences between primary cutaneous neoplasms and the other groups were only significant for staining with HECA-452.

Discussion

The results of this study indicate that, analogous to benign chronic inflammatory infiltrates in skin, the CLA+ memory T-cell subset preferentially infiltrates cutaneous neoplasms. CLA+ T-cell infiltrates were characteristic of both squamous cell carcinoma and melanoma primaries of the skin but were not evident in metastatic foci of these tumors, including metastases to dermis. These observations suggest that 1) the growth of primary tumors likely invokes a similar, if not identical, inflammatory response as

Table 1. *Immunohistochemical Profiles of the Tumor Immune Response*

Histological Diagnosis	Antibody (mean% ± s.d.) L26	Leu-22	OPD4*	HECA-452
Primary malignant melanoma (n = 11)	2.5 ± 4.7	97.3 ± 4.7	54.0 ± 19.1	48.6 ± 21.1
Primary squamous cell carcinoma (n = 9)	4.7 ± 5.7	95.3 ± 5.7	55.0 ± 28.5	45.0 ± 19.3
Cutaneous primaries metastatic to skin (n = 2)	5.0 ± 7.1	95.0 ± 7.1	82.5 ± 3.5 / 2.5 ± 3.5	0
Cutaneous primaries metastatic to other sites (n = 4)	1.3 ± 2.5	98.8 ± 2.5	63.8 ± 14.9 / 3.3 ± 5.8	0
Noncutaneous primaries metastatic to skin (n = 3)	3.3 ± 5.8	96.7 ± 5.8	63.3 ± 15.3 / 3.3 ± 2.9	0
Noncutaneous primaries metastatic to other sites (n = 2)	17.5 ± 17.7	82.5 ± 17.7	70 ± 28.3 / 2.-5 ± 3.5	0

* When present, the numerator denotes lymphocytes at periphery and the denominator lymphocytes within the tumor.

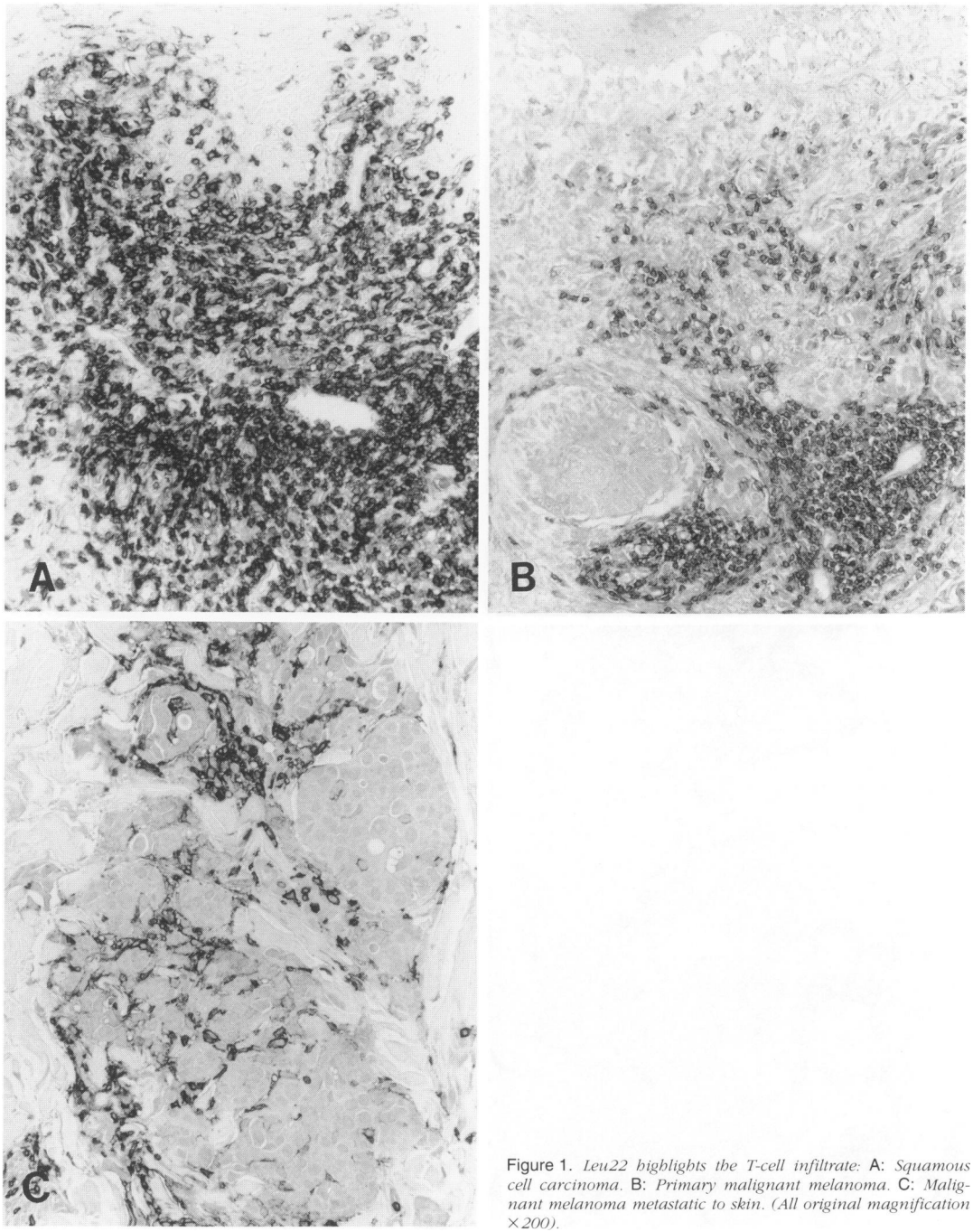

Figure 1. *Leu22 highlights the T-cell infiltrate:* A: *Squamous cell carcinoma.* B: *Primary malignant melanoma.* C: *Malignant melanoma metastatic to skin. (All original magnification ×200).*

non-neoplastic immune/inflammatory stimuli and 2) an intact normal epidermis was required for the selective recruitment of the CLA+ T-cell subset.

The overall lower percentage of CLA+ T cells found associated with cutaneous tumors in this study compared to previous studies of benign dermatoses (55% versus 85% CLA+) is undoubtedly due to methodological differences between the two studies, specifically the decreased sensitivity of HECA-452 staining in paraffin sections versus cryostat sections. Flow cytometric studies indicate that CLA is expressed in a continuous range of densities among positive T cells, and thus, the threshold for calling a cell positive depends on the sensitivity of the method selected.[2,3] Indeed, T cells obtained from skin blisters overlying delayed hypersensitivity reactions were essentially all CLA+ (although of varying intensities) when examined by high-

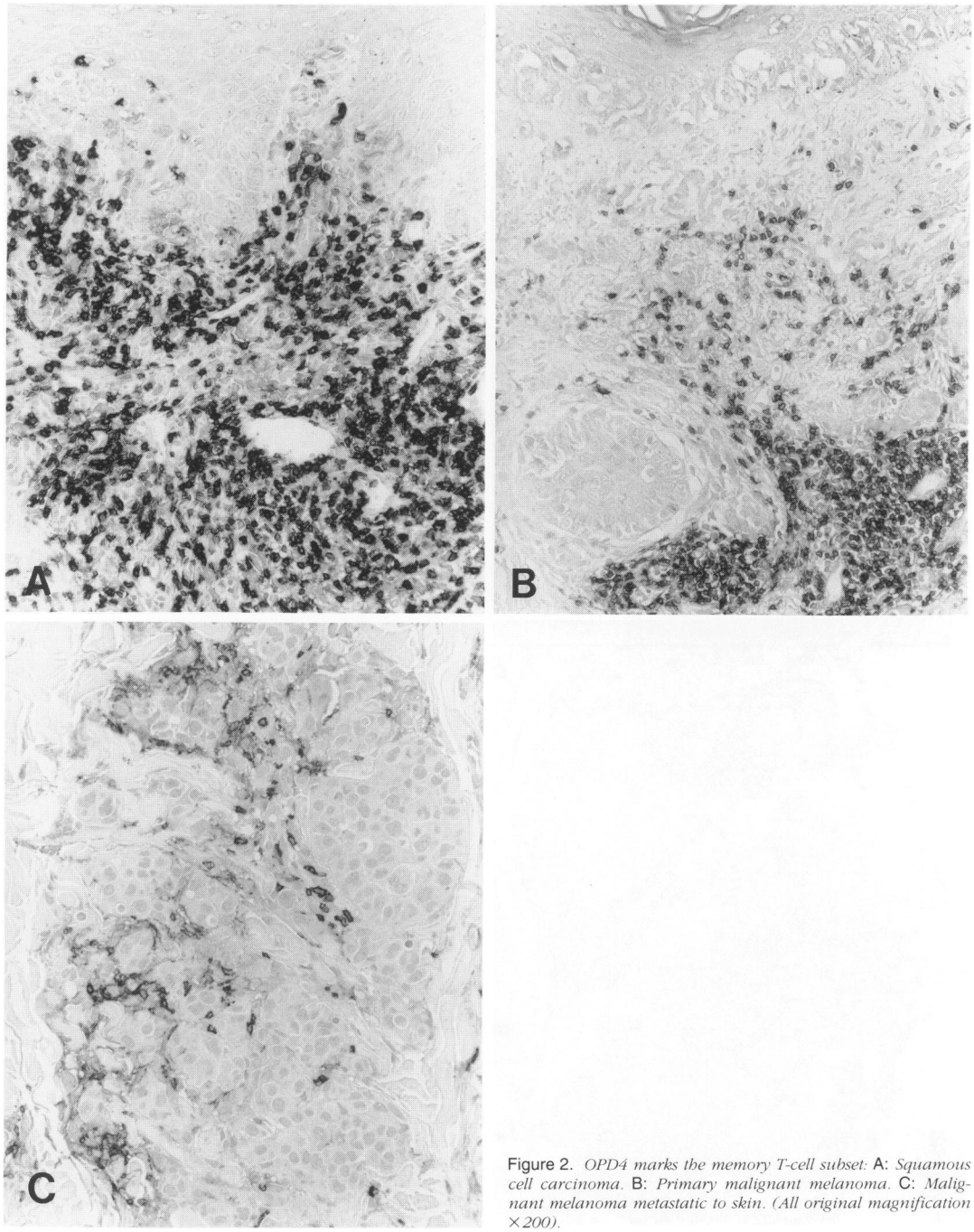

Figure 2. *OPD4 marks the memory T-cell subset:* A: *Squamous cell carcinoma.* B: *Primary malignant melanoma.* C: *Malignant melanoma metastatic to skin. (All original magnification ×200).*

resolution flow cytometry.[13] The decreased sensitivity of paraffin sections is, however, more than compensated for by the increased availability of archival specimens and by the superior morphology afforded by the paraffin immunohistology. Morphological clarity allows the discrimination and elimination of consideration of nonlymphocyte reactivity with the HECA-452 antibody.

CLA has been shown to be *selectively* expressed on memory T cells in sites of cutaneous inflammation and on the malignant T cells of mycosis fungoids.[2] The significance of this selective expression became clear when it was determined that 1) CLA is expressed on a subset of memory T cells in peripheral blood and on essentially all T cells infiltrating cutaneous inflammatory sites, including the ini-

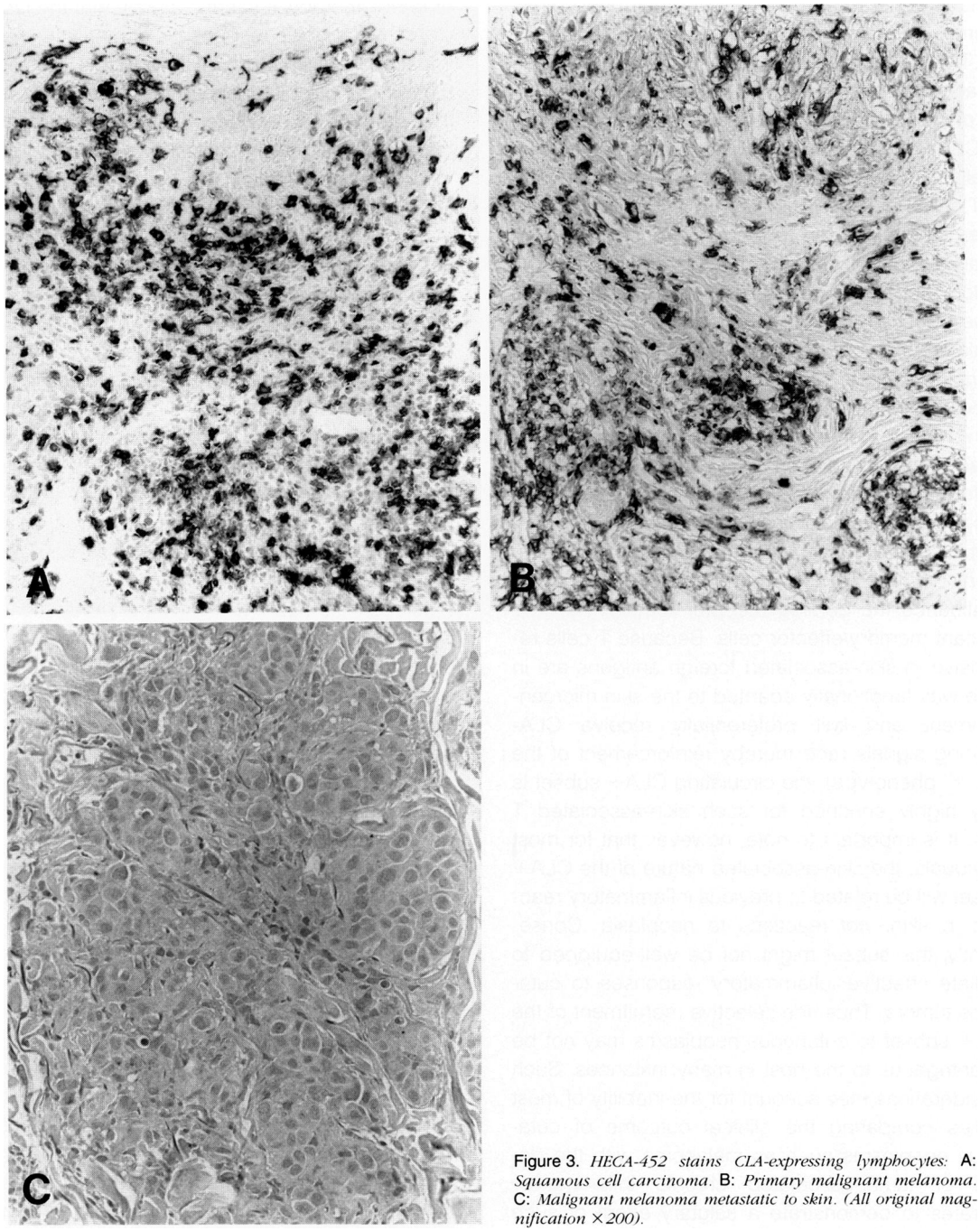

Figure 3. *HECA-452 stains CLA-expressing lymphocytes:* A: *Squamous cell carcinoma.* B: *Primary malignant melanoma.* C: *Malignant melanoma metastatic to skin. (All original magnification ×200).*

tial T-cell influx into these sites; 2) CLA is the T-cell ligand for the vascular selectin E-selectin; and 3) E-selectin is preferentially expressed on dermal venules in the setting of chronic (mononuclear cell) inflammation.[1,4,13] Taken together, these data strongly suggested that the predominant mechanism mediating the selective expression of CLA on cutaneous T cells is the selective homing of these cells into the skin and that CLA and E-selectin likely function as a lymphocyte homing receptor-endothelial ligand pair that preferentially targets a distinct subset of memory/effector T cells to the skin.

The finding of a preferential CLA+ T-cell infiltration in cutaneous tumors provides further support for this hypothesis and, in addition, offers new in-

sights into the immunobiology of these neoplasms. Whereas it is clear from several lines of evidence that T-cell extravasation at sites of inflammation is *not* antigen-specific, recent studies on the regulation of CLA have suggested mechanisms by which the CLA+ memory T-cell subset may become functionally skin-associated.[1] CLA is not present on virgin T cells but is up-regulated on a subset of T cells undergoing the virgin to memory transition in secondary lymphoid tissues. This up-regulation is not random but seems to occur in a highly regulated, tissue-selective manner.[13] For example, CLA is up-regulated on over half of the T cells undergoing the virgin to memory transition in skin-associated peripheral lymph nodes but on fewer than 10% of transition T cells in the mucosal microenvironment of the appendix. In addition, CLA expression seems to be further up-regulated when memory/effector T cells are reactivated in the cutaneous microenvironment.[13] These observations indicate that local microenvironments at the time of T-cell activation act to influence the homing receptor repertoire of the resultant memory/effector cells. Because T cells responsive to skin-associated foreign antigens are in some way functionally adapted to the skin microenvironment and will preferentially receive CLA-inducing signals (and thereby reinforcement of the CLA^{high} phenotype), the circulating CLA+ subset is likely highly enriched for such skin-associated T cells. It is important to note, however, that for most individuals, the skin-associated nature of the CLA+ subset will be related to previous inflammatory reactions in skin, *not* reactions to neoplasia. Consequently, this subset might not be well-equipped to mediate effective inflammatory responses to cutaneous tumors. Thus, the selective recruitment of the CLA+ subset to cutaneous neoplasms may not be advantageous to the host in many instances. Such considerations may account for the inability of most studies comparing the clinical outcome of cutaneous neoplasms such as melanoma with the degree of tumor-associated chronic inflammatory infiltrates to demonstrate a salutary effect of such infiltrates.[14–17]

A second significant implication of this study concerns the regulation of the skin-selective homing specificity. The critical observation here is the finding that primary malignancies of both the keratinocyte and melanocyte were accompanied by a predominant CLA+ T-cell infiltrate, whereas metastatic foci of these same tumor types to both cutaneous and extracutaneous sites were not associated with this T-cell subset. Because these patients were clinically well and had not received either radiotherapy or chemotherapy, it seems unlikely that the lack of a CLA+ lymphocyte response is primarily the result of impaired host immunity. It is possible that primary tumors of both histogenetic origins secrete factors that promote CLA+ T-cell infiltration, whereas metastases, which likely constitute a subset of the primary tumor population, do not. However, the most likely explanation for these observations stems from the fact that all the primary tumors examined were associated with involvement of non-neoplastic epidermis. In contrast, the metastatic foci in skin were exclusively dermal in location, and, of course, the extracutaneous metastases were far from normal epidermis. Thus, it is likely that the selective recruitment of the CLA+ memory T-cell subset to cutaneous tumors requires tumor involvement (or irritation) of the normal epidermis. As indicated above, one key element of the recruitment of CLA+ T-cells to skin is the up-regulation of E-selectin expression by venules of the superficial dermal vascular plexus.[4,5] In inflammatory lesions of the skin, the induction of E-selectin is thought to involve the production of the interleukin-1 and/or tumor necrosis factor-α by keratinocytes with or without the assistance of dermal mast cells.[18–21] Additional epidermal derived factors, perhaps acting as chemoattractants, may be necessary to promote the influx of the CLA+ T-cell subset as well. Both melanoma and squamous cell carcinoma cells may lack one or more of these required elements and thus lack the ability selectively to recruit CLA+ T cells by themselves. However, upon irritation of local normal epidermis, all required elements are produced.

This situation is somewhat different than what has been described for another tissue-selective T-cell surface antigen—the mucosal lymphocyte-associated antigen (MLA; defined by monoclonal antibodies HML-1 and Ber ACT8).[3,22,23] MLA has recently been characterized as a member of the integrin adhesion molecule family that is composed of a novel integrin α-chain (αe) associated with the β7-chain.[24,25] Its function is unknown, but it is clearly selectively expressed on intraepithelial and lamina propria T cells of the mucosal tract. Like CLA, MLA is also preferentially expressed by T cells associated with primary epithelial malignancies of the gastrointestinal tract.[26] However, the MLA determinant is also found on T cells associated with metastatic foci of gastrointestinal carcinomas in the liver, a finding suggesting normal mucosal epithelium is not required for its presence.[26] MLA has not been clearly shown to be a homing receptor, and it is unclear whether its selective expression is due to tissue-selective homing or to selective up-regulation

within the mucosal microenvironment. In any case, mucosal carcinomas seem to have the capability either to attract this subset or up-regulate MLA expression by themselves, in contrast to the situation with CLA and epidermal tumors.

In summary, the results of this study suggest that the local cutaneous immune response to tumors is characterized by preservation of normal mechanisms of lymphocyte homing to inflamed skin, namely, the selective recruitment of the CLA+ memory T-cell subset. In other words, tumors do not seem to recruit unique tumor-associated T-cell populations. An implication of this observation concerns strategies designed to treat tumors via modulation of host immune responses or by adoptive immunotherapy. These results suggest a critical need to take into consideration the usual mechanisms of lymphocyte recruitment to the tumor being treated. Failure to do so may obviate potential therapeutic benefits by resulting in inefficient effector cell localization at the appropriate sites. On the other hand, increased therapeutic efficacy may result from procedures designed to produce lymphocyte effector populations with homing receptor repertoires compatible with a given tumor's vascular bed.

Acknowledgments

The authors thank Eugene C Butcher, M.D. and David P LeBrun, M.D., for their thoughtful comments, Jerry Halpern, Ph.D., for consultative advice with biostatistics, Eva A Pfendt for technical assistance with immunohistochemistry, and Phil Verzola for technical assistance with photography.

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